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Beyond dyspnoea as an endpoint in acute heart failure trials

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This editorial refers to ‘Early dyspnoea relief in acute heart failure: prevalence, association with mortality, and effect of rolofylline in the PROTECT Study’[†], by M. Metra et al., on page 1519

Acute heart failure syndromes (AHFS) has been defined as new onset or recurrence of gradually or rapidly worsening signs and symptoms of heart failure (HF) necessitating urgent or emergency therapeutic intervention.¹ The number of hospitalizations for AHFS continues to increase and they account for ~1 million admissions annually in both Europe² and the USA.³ Dyspnoea is the most common presenting symptom among patients hospitalized for AHFS,^{4,5} making it a clinically relevant therapeutic target and endpoint for clinical trials and regulatory approval.^{6–8} Although dyspnoea and other signs and symptoms of HF appear to improve in response to standard therapy alone during initial stabilization⁴ and hospitalization,^{9–11} many patients are being sent home with persistent signs and symptoms of HF.¹² In addition, the post-discharge mortality and HF rehospitalization rate remain as high as 15 and 30%, respectively, within 60–90 days.¹³ Thus, there is a critical unmet need in AHFS to develop novel agents capable of safely improving signs and symptoms of HF beyond standard therapy during hospitalization and reducing the early post-discharge event rate.¹⁴

Metra et al.¹⁵ address whether dyspnoea relief predicts short-term morbidity and mortality in a *post-hoc* analysis of the Placebo-controlled Randomized Study of the Selective A₁ Adenosine Receptor Antagonist Rolofoylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial.¹⁶ The PROTECT trial enrolled patients hospitalized for AHFS and characterized by the following: (i) normal or reduced ejection fraction (EF); (iii) persistent dyspnoea at rest or with minimal activity; (iii) a creatinine clearance of 20–80 mL min⁻¹; (iv) a B-type natriuretic peptide (BNP) level ≥500 pg mL⁻¹ or an N-terminal pro-BNP level ≥2000 pg mL⁻¹; and (v)

requiring intravenous (i.v.) loop-diuretic therapy. Participants were randomly assigned to receive 30 mg of i.v. rolofylline once daily or matching placebo for up to 3 days. Compared with placebo, rolofylline did not improve a composite primary endpoint assessing for death or HF rehospitalization, signs and symptoms of HF requiring therapeutic intervention, or worsening renal function.

In the retrospective analysis of the PROTECT trial,¹⁵ Metra and colleagues examined the association between early dyspnoea relief, defined as moderate or marked improvement at both 24 and 48 h post-study drug administration, and changes in body weight and mortality at day 14 and 30. This study makes the following clinically important contributions to our understanding of the clinical course of patients hospitalized for AHFS:

- (i) Somewhat similarly to previous studies,^{4,9–11} ~50% of patients did not experience moderate or marked dyspnoea relief, suggesting that there is room for new therapies to improve signs and symptoms of HF in this patient population.
- (ii) This analysis confirms a key observation from the EVEREST trial,⁹ namely the correlation between weight loss during hospitalization and dyspnoea relief.
- (iii) Early dyspnoea relief emerges as an important clinical marker for post-discharge survival.
- (iv) Dyspnoea relief was not associated with changes in renal function during hospitalization, suggesting that these changes in renal function should not be part of a composite endpoint in AHFS trials.

However, the most important outcome of this analysis is the finding that early dyspnoea relief was associated with decreased post-discharge mortality even after adjusting for known predictors of prognosis including age, New York Heart Association (NYHA) functional class, serum creatinine, serum sodium, serum BNP, and blood pressure. This is an intriguing observation which generates the hypothesis that dyspnoea may be a suitable surrogate for safety and/or an endpoint for mortality in AHFS trials. Assuming

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the finding to be valid, dyspnoea would be the ideal primary endpoint for AHFS clinical trials, serving as an indicator of both symptomatic improvement during hospitalization and morbidity and mortality in the early post-discharge 'vulnerable' period. In terms of clinical trial design, utilizing dyspnoea as a substitute marker for mortality would require recruiting fewer patients to conduct a meaningful and appropriately powered study, greatly reducing the financial burden of new drug development.

However, there are several shortcomings of the data that question the internal and external validity of this conclusion. Retrospective multivariate analysis, by definition, is intrinsically limited by the inability of the model to correct for unmeasured or unknown confounders. Although the authors adjusted for a number of potential confounders, their multivariate model did not adjust for left ventricular ejection fraction (LVEF), baseline β -blocker, or angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) utilization at admission, or inotrope usage or diuretic dose during hospitalization. In fact, patients reporting early dyspnoea relief were more likely to be on a β -blocker or an ACE inhibitor/ARB at the time of admission and less likely to receive oral or i.v. inotropes during hospitalization. These observations suggest that patients experiencing early dyspnoea relief have less severe HF at baseline and may partially or completely explain the association between early dyspnoea relief and improved survival.

The larger scientific question is whether or not there are any reliable surrogate endpoints for mortality in AHFS trials. Pivotal clinical trials in AHFS with mortality as an endpoint for safety and/or efficacy are onerous, logistically complicated, and expensive to conduct, making it desirable to find a suitable candidate surrogate marker for safety and/or mortality. Unfortunately, the available data suggest that improvements in major clinical predictors of prognosis including body weight, serum sodium, renal function parameters, levels of neurohormones, central haemodynamics, etc. do not translate clinically into a direct mortality benefit (Table 1).¹⁷

Essentially, indicators of prognosis may not necessarily be causative mediators. In addition, a mediator of outcome for one therapeutic intervention may not be a mediator for another novel agent since known or unknown side effects may obscure any putative beneficial effects. Thus, we believe that early dyspnoea relief, even if it is predictive of prognosis in this patient population, may not be an appropriate surrogate for mortality when studying novel therapies. For example, in REVIVE II,¹⁸ levosimendan treatment facilitated dyspnoea relief, which did not correlate with improved post-discharge outcomes, because levosimendan treatment was also associated with a propensity for atrial and ventricular arrhythmias and increased mortality.

Although intriguing, at the present time dyspnoea is not a substitute for clinical outcomes such as HF rehospitalization and mortality as an endpoint for safety and/or efficacy in AHFS clinical trials. However, dyspnoea is the most prevalent presenting symptom in patients hospitalized for HF and thus an important measure of symptomatic improvement, and continues to be an approval endpoint for the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).¹⁵ Thus, dyspnoea will continue to serve as an efficacy endpoint for short-term symptomatic relief.

However, the importance of dyspnoea as a primary endpoint should be critically evaluated for the following reasons:

- Standard therapy: the available data suggest that standard therapy alone appears to relieve dyspnoea and other signs and symptoms of HF.^{4,9–11} In fact, patients not experiencing immediate symptomatic improvement often respond to additional strategies such as repeated boluses of i.v. loop diuretics. As a result, it may be very difficult to 'beat' standard therapy safely. However, the *post-hoc* analysis by Metra *et al.* suggests that dyspnoea may not always be sufficiently treated in at least a subset of patients hospitalized for AHFS.
- When to measure: global registry⁴ and clinical trial^{9–11} data have shown that the majority of patients are no longer severely dyspnoeic after 6 h of standard therapy alone unless provoked (orthopnoea).¹⁹ However, it should be noted that many trials employing baseline dyspnoea as an inclusion criterion and dyspnoea reduction as an endpoint have enrolled patients later (up to 48 h after admission),¹¹ potentially by design leading to the selection of the patients most refractory to standard therapy and more likely to present with lower blood pressure and baseline renal dysfunction, clinical characteristics which may influence the effects of the agent being tested.
- How to measure: despite the fact that dyspnoea has played a prominent role as an endpoint in AHFS clinical trials and the regulatory approval process, most studies have not used a standardized method (posture, supplemental oxygen status, etc.) to assess dyspnoea and ensure the reproducibility of data collection. However, a standard method to measure dyspnoea was proposed relatively recently.²⁰
- Correlation with a pathophysiological mechanism: patients with a very high pulmonary capillary wedge pressure (PCWP) may experience minimal dyspnoea, while patients with a relatively lower PCWP may be severely dyspnoeic.²¹ This observation is complicated by the fact that HF rarely occurs in isolation and is frequently accompanied by medical co-morbidities (e.g. chronic obstructive pulmonary disease), which may contribute to the overall dyspnoeic state through additional pathophysiological mechanisms. As a result, the severity of dyspnoea may be loosely associated with other signs and symptoms of HF, such as jugular venous distension (JVD) and oedema.
- International variation: it is essential to recognize that dyspnoea is a self-reported symptom and this subjective sensation may be perceived very differently by different patient populations. This hypothesis is further substantiated by the URGENT-dyspnoea registry,⁴ which revealed that baseline dyspnoea and management show regional differences, implying that results from clinical trials conducted in one region may not be generalized to another.²²

In conclusion, the high prevalence of dyspnoea in patients presenting with AHFS underscores its importance as a primary efficacy endpoint for short-term symptomatic improvement in AHFS clinical trials and the regulatory approval process. If dyspnoea continues to be an important endpoint for short-term efficacy it should be measured early, using uniform methods (i.e. provoked and off oxygen), and correlated with other relevant clinical signs and symptoms of congestion and biomarkers such as troponin

Table 1 Selected prognostic markers as targets of HF clinical trials

	Prognostic marker/ predictor	Intervention	Duration of intervention/ time of assessment	Outcomes: mortality
Haemodynamics	Yes	Epoprostenol (FIRST) Nesiritide (VMAC)	Long/short Short/short	No benefit No benefit ^a
Neurohormones	Yes (BNP)	Levosimendan (REVIVE/SURVIVE)	Short/long	No benefit ^b
	Yes (Norepinephrine)	Moxonidine (MOXCON/MOXSE)	Long/long	Worse
	Yes (Endothelin)	Tezosentan (VERITAS)	Short/short	No benefit
	Yes (TNF)	Etanercept (RECOVER/RENAISSANCE) ^c	Long/long	No benefit
Renal function	Yes (BUN, Cr, eGFR)	Milrinone (OPTIME-CHF)	Short/long	No benefit
Serum sodium	Yes	Tolvaptan (EVEREST)	Long/long	No benefit
Body weight	Yes	Tolvaptan (EVEREST)	Long/long	No benefit
QRS duration	Yes	CRT (CARE-HF) ^c	Long/long	Positive

Duration of intervention (how long therapy was given): short indicates with hospitalization only; long indicates continued post-discharge or as outpatient. Time of assessment (when assessment of prognostic marker occurred): short indicates <7 days; long indicates >7 days.

^aRetrospective trend towards increased mortality.

^bThe REVIVE trial showed a trend toward an increase in early mortality.

^cChronic HF trials.

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; CRT, chronic resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; TNF, tumour necrosis factor.

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and possibly BNP. It is noteworthy that the majority of clinical trials conducted in AHFS to date have been negative in terms of efficacy and/or safety. Clinical trials have been classified as Stage A (short-term therapy started during initial stabilization in the emergency department), B (short-term medications aimed at signs and symptoms remaining despite initial therapy), and C (long-term therapies initiated during hospitalization and continued post-discharge).¹

Although it is clear that for Stage C clinical trials, mortality and/or morbidity (HF rehospitalization, etc.) should be the primary efficacy endpoint, it is unlikely that short-term therapeutic interventions tested in Stage A and B clinical trials will reduce post-discharge mortality unless the short-term therapy prevents myocardial and/or renal injury, which may occur in a subset of AHFS patients.²³ Given the limitation of utilizing dyspnoea alone as a primary endpoint, an appropriate efficacy endpoint for a Stage A and B clinical trial may be a clinical composite.²⁴

Any endpoint that focuses on a single symptom, such as dyspnoea alone, at a single point in time ignores other symptoms and/or biomarkers of congestion and/or myocardial injury that may be highly relevant to the patient and neglects the possibility that any benefits may be minor or transient. Hence, a clinical composite (including dyspnoea) may address many of the disadvantages and biases inherent in an endpoint that focuses on a single symptom at a single point in time. In the 'clinical composite approach', the patient must report moderate or marked improvement early in the course of therapy, and such improvement must be sustained throughout the entire duration of the drug's presence in the body.

In addition, in the conventional approach, a patient who deteriorates and improves solely because of intensification of background therapy can be considered to be clinically improved. In contrast, the clinical composite minimizes the noise created by the intensification of background therapy by excluding from the category of

improvement those patients whose improvement could be ascribed solely to the use of background therapy (because they showed symptomatic deterioration during treatment with the study medication). Finally, in the conventional approach, a patient who deteriorates and drops out of the study could be excluded from analyses that focus on the clinical status of patients who complete the study. In contrast, the clinical composite minimizes the bias inherent in a 'completers' analysis by including all patients in the primary analysis (according to the intention-to-treat principle), particularly those who dropped out of a study because of worsening of their clinical course. Thus, composite endpoints that take into account not only signs and symptoms but also improvement, or at least preservation, of organ function (e.g. heart and kidney) may serve as a potential basis for regulatory approval as long as symptom relief does not occur at the expense of longer term safety with the degree of 'acceptable' risk related to the degree and type of benefit.

Conflict of interest: F.R. has acted as a consultant to the company 'Cardiorentis'.

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